EXHIBIT B

Confidential Information
REDACTED

CONFIDENTIAL–OUTSIDE ATTORNEYS' EYES ONLY

Tracey B. Davies (pro hac vice)
tdavies@gibsondunn.com
MARK REITER (PRO HAC VICE)
mreiter@gibsondunn.com
GIBSON, DUNN & CRUTCHER LLP
555 Mission Street, Suite 3000
San Francisco, CA 94105-0921
Telephone: 415.393.8200
Facsimile: 415.393.8306

Attorneys for *Defendant NATERA, INC.*

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

ILLUMINA, INC.,

Plaintiff,

v.

NATERA, INC.,

Defendant.

CASE NO. 3:18-CV-01662-SI

DEFENDANT NATERA, INC.'S SECOND AMENDED INVALIDITY CONTENTIONS UNDER PATENT L.R. 3-3

CONFIDENTIAL –

OUTSIDE ATTORNEYS' EYE ONLY

I. INTRODUCTION

Pursuant to Patent L.R. 3-3 and 3-6, Defendant Natera, Inc. ("Natera") hereby submits to Plaintiff Illumina, Inc. ("Illumina") the following Second Amended Invalidity Contentions regarding U.S. Patent No. 9,493,831 (the "'831 patent").

Illumina asserted infringement of claims 1-3, 6-10, 13-22, and 24 of the '831 patent (collectively, the "Asserted Claims"). Should Illumina contend that any limitation of the Asserted Claims is not disclosed in the art identified by Natera as anticipatory, Natera reserves the right to identify references that, together with the prior art disclosed, would have rendered obvious the Asserted Claim(s). Additionally, should Illumina provide evidence or contentions regarding secondary considerations of non-obviousness pertaining to the Asserted Claims, Natera reserves the right to challenge such evidence or contentions.

Natera's investigation into the prior art—including prior art identified in these disclosures, third-party prior art, and related evidence, documents, and knowledgeable witnesses (fact and expert)—remains continuing and ongoing. As a result, additional prior art may come to light. Furthermore, additional prior art may become relevant depending on Natera's further understanding of Illumina's infringement contentions. Additional information and evidence about prior art, including documentation and witness testimony, may later be discovered and presented. Accordingly, Natera reserves the right to present this additional information and evidence in support of its invalidity contentions, and to amend and supplement these contentions accordingly in a manner consistent with the Federal Rules of Civil Procedure and the Court's rules, including the Patent Local Rules.

II. INVALIDITY CONTENTIONS

Pursuant to Patent L.R. 3-3, Natera provides the following information with respect to the Asserted Claims. Each one of the Asserted Claims is invalid because it fails to meet the patentability requirements under 35 U.S.C. §§ 101, 102, 103, and 112. Unless otherwise indicated, for purposes of Natera's invalidity contentions, the priority date for the '831 patent is taken to be no earlier than January 23, 2010—based on Illumina's infringement contentions under Patent L.R. 3-1, served on July 6, 2018. Natera does not concede or admit that Illumina is entitled to that date for purposes of priority, and Natera reserves all rights to establish and/or challenge that Illumina is not entitled to any of the priority

dates that it has asserted or will assert in this action. In addition, Natera contends that the Asserted Claims of the '831 patent introduce new matter that is not supported by the written descriptions of the earlier patent applications, U.S. Patent Application No. 13/792,661 (filed March 11, 2013), U.S. Patent Application No. 13/012,222 (January 24, 2011), and U.S. Provisional Patent Application No. 61/297,755 (filed January 23, 2010), as described below in Section II.D. Thus, these claims are not entitled to the benefit of any of the filing dates of those earlier applications. Natera reserves the right to modify, amend, and/or supplement Natera's invalidity contentions if any Asserted Claim of '831 patent is determined to be entitled to a priority date later than January 23, 2010.

As explained above, discovery is ongoing and additional prior art may be located and thus Natera reserves the right to supplement its invalidity contentions if additional prior art is located.

A. Patent L.R. 3-3(a)

Claims 1-3, 6-10, 13-22, and 24 of the '831 patent are invalid as anticipated under 35 U.S.C. § 102 or obvious under 35 U.S.C. § 103 by the prior art references and work listed or identified below and/or described in the claim charts attached hereto and incorporated as Exhibits 1–14. In addition to establishing invalidity, the research, publications and contributions referenced herein establish the state of the art at the relevant time.

1. Prior Art Patents and Publications

In Appendix A attached hereto, Natera identifies prior art patents and publications that Natera contends anticipate and/or render obvious the Asserted Claims of the '831 patent.

2. Public Use, Prior Knowledge, and Prior Sale

Natera identifies below prior art systems, platforms, assays, and/or kits that were publicly sold, offered for sale, and/or disclosed prior to January 23, 2010:

Platforms, Assays, or Kits	Year of Disclosure or Sale
Roche/454 Life Sciences Genome Sequencer Systems	2005
Roche/454 GS library preparation kits, including without limitation, GS FLX Titanium General Library Preparation Kit; GS FLX Titanium Rapid Library Preparation Kit; GS FLX Titanium emPCR Kits; GS FLX Titanium emPCR Breaking Kits; GS FLX Titanium Sequencing Kit; GS FLX Titanium PicoTiter Plate Kit	2005-2009

Illumina/Solexa Genome Analyzer (GA) Systems	2006
Illumina's Library Preparation Kit for the Illumina GA Sequencers, including without limitation, Illumina Multiplexing Sample Preparation Oligonucleotide Kit; Illumina Multiplexing Sequencing Primers and PhiX Control Kit; Illumina Paired-End Genomic DNA Sample Prep Kit; Illumina Genomic DNA Sample Prep Kit	2006-2009
Life Technologies SOLiD Sequencers and Library Prep Kits	2007
Helicos Genetic Analysis Systems	January 2009
Illumina Golden Gate Assay	2004 or earlier
Febit's HybSelect	March 2009
Agilent SureSelect Target Enrichment System	February 2009
Agilent Capture Array	July 2009
Roche/NimbleGen SeqCap	October 2009
Roche/NimbleGen Array Capture	July 2008
RainDance Technologies RainStorm™ Microdroplet Technology	December 2008
Fluidigm Access Array	June 2009

In the table above, Natera provides the names of the platforms, assays, and kits as well as their dates of disclosure and/or sale currently known to Natera after a reasonable search. Third-party discovery is ongoing, and additional evidence demonstrating the prior use, prior disclosure, and/or prior sales and their respective dates will be provided as it is collected.

3. Prior Invention

The Asserted Claims of the '831 patent are invalid under 35 U.S.C. § 102(g) because the method of preparing a targeted sequencing library from cell-free DNA in maternal blood samples for fetal aneuploidy determination was invented by others in this country before Yue-Jen Chuu and Richard P. Rava, the alleged inventors of the '831 patent.

Discovery is likely to show that one or more of the following individuals conceived of and reduced to practice, without abandoning, suppressing, or concealing, the subject matter claimed in the '831 patent prior to the '831 patent inventors' alleged conception and reduction to practice the subject

matter: Stephen Quake and Hei-Mun Christina Fan. Exhibits 2 and 10 show exemplary evidence of prior invention by Dr. Quake at Stanford University and his collaborators. Additional evidence may be found in the records for the following patent interferences: *Quake v. Lo*, No. 105,920 (P.T.A.B. Apr. 7, 2014); *Lo v. Quake*, No. 105,923 (P.T.A.B. Apr. 7, 2014); and *Lo v. Quake*, No. 105,924 (P.T.A.B. Apr. 7, 2014). Exhibits 15 and 16 shows exemplary evidence of prior invention by Fluidigm Corporation and Bio-Rad Laboratories, respectively.

In addition, the Asserted Claims of the '831 patent are invalid under 35 U.S.C. § 102(g) because one or more employees at Natera, Inc. (formerly known as Gene Security Network), performed and/or offered in this country, without abandoning, suppressing or concealing, the claimed methods of the '831 patent before the '831 inventors' alleged conception and reduction to practice. For example, International Patent Application Publication No. WO 2008/115497, titled "System and method for cleaning noisy genetic data and determining chromosome copy number," discloses a method of determining fetal aneuploidy using cell-free DNA from maternal blood samples and targeted sequencing. Exhibit 14 on WO 2008/115497 shows exemplary evidence of prior invention by one or more of the Natera employees.

Moreover, the Asserted Claims of the '831 patent are invalid under 35 U.S.C. § 102(g) because one or more employees at Fluidigm Corporation, performed and/or offered in this country, without abandoning, suppressing or concealing, the claimed methods of the '831 patent before the '831 inventors' alleged conception and reduction to practice. Exhibit 15 shows exemplary evidence of prior invention by one or more of the Fluidigm employees. [redacted] In addition, U.S. Patent Publication 2010/0120038 ("Fluidigm") teaches methods to improve the preparation of DNA sequence libraries, which can be used in sequencing reactions to detect certain sequences. Ex. 1. At least one of the library preparation methods of Fluidigm discloses the three amplification steps of the '831 patent. Specifically, the method entitled "Detection of Multiple Target Nucleic Acids-Modular Approach"

employs three targeted amplification steps. When used to produce a sequencing library, the "Modular Approach" falls within the scope of the Asserted Claims.

The Asserted Claims of the '831 patent are also invalid under 35 U.S.C. § 102(g) because one or more employees at Bio-Rad Laboratories performed and/or offered in this country, without abandoning, suppressing or concealing, the claimed methods of the '831 patent before the '831 inventors' alleged conception and reduction to practice. [redacted] Exhibit 16 shows exemplary evidence of prior invention by one or more of the Bio-Rad Laboratories employees.

Lastly, the Asserted Claims of the '831 patent are invalid under 35 U.S.C. § 102(g) because one or more employees at Sequenom Inc. performed and/or offered in this country, without abandoning, suppressing or concealing, the claimed methods of the '831 patent before the '831 inventors' alleged conception and reduction to practice. For example, U.S. Patent Application No. 13/518,368 (filed on February 6, 2013 and published as U.S. Patent Publication 2013/0130923 ("Ehrich")) claims the benefit of U.S. Provisional Patent Application No. 61/289,370 (filed on December 22, 2009). Ehrich teaches a method of analyzing chromosomal abnormality using cell-free DNA from maternal blood samples and discusses generating a sequencing library using targeted sequence enrichment and nested PCR. Exhibit 8 on Ehrich shows exemplary evidence of prior invention by one or more of the Sequenom employees.

B. Patent L.R. 3-3(b)

1. Obviousness

As set forth in the accompanying claim charts and explained below, the references identified in Exhibits 1–16, considered alone or in combination, invalidate the claims as obvious under 35 U.S.C. § 103. In addition, to the extent that the prior art references, platforms, and/or kits identified in Section II.A above do not explicitly or inherently anticipate any claim, Natera contends that any difference between that prior art and the Asserted Claims would have been obvious to one of ordinary skill in the

art, either alone or in combination with other references. Exemplary combinations of prior art references, prior platforms and kits that render the '831 patent obvious are listed below and attached hereto as Exhibits 1–16.

- **Ex. 1.** Claims 1-3, 5-10, 13-22, and 24 are anticipated and/or rendered obvious by Fluidigm in view of the knowledge of a person of ordinary skill (as reflected, redundantly, in Fan, Chiu, Bentley, Quail, and the Illumina Datasheet), and further in view of Sequenom
- **Ex. 2.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Fan 2008 in view of the knowledge of a person of ordinary skill, and further in view of the '575 Publication and/or the Illumina DataSheet
- **Ex. 3.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Chiu in view of the knowledge of a person of ordinary skill, and further in view Tewhey and/or the Illumina DataSheet
- **Ex. 4.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Hamilton in view of the knowledge of a person of ordinary skill in the art, and further in view of the '575 Publication and/or the Illumina DataSheet
- **Ex. 5.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Dube in view of the knowledge of a person of ordinary skill in the art, and further in view of the '575 Publication and the Illumina DataSheet
- **Ex. 6.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Shoemaker in view of the knowledge of a person of ordinary skill in the art, and further in view of the '575 Publication and/or the Illumina DataSheet
- **Ex. 7.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Cuppens in view of the knowledge of a person of ordinary skill in the art, and further in view of Sequenom and/or Quail
- **Ex. 8.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Ehrich in view of the knowledge of a person of ordinary skill in the art, and in further view of Varley 2009
- **Ex. 9.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Lo 2007 in view of the knowledge of a person of ordinary skill and/or the '330 Publication and Illumina DataSheet

- **Ex. 10.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Fan 2007 in view of the knowledge of a person of ordinary skill and/or the '525 Publication, '575 Publication, and Illumina DataSheet
- **Ex. 11.** Claims 1-3, 6-10, 13-22, and 24 are invalid for non-statutory double patenting
- **Ex. 12.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Hybrid Capture Array Technology (Agilent's SureSelect, Agilent's Capture Array, Roche's NimbleGen SeqCap, Roche's NimbleGen Capture Array, and Febit's HybSelect) in view of the knowledge of a person of ordinary skill in the art, and further in view of the '575 Publication and/or the Illumina DataSheet
- **Ex. 13.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Targeted PCR Technology (Raindance PCR Technology, Illumina's GoldenGate, and Fluidigm Access Array) in view of the knowledge of a person of ordinary skill in the art, and further in view of Chiu and/or NGS Technology
- **Ex. 14.** Claims 1-3, 6-10, 13-22, and 24 are rendered obvious by Rabinowitz in view of the knowledge of a person of ordinary skill in the art, and further in view of Targeted PCR and/or NGS Technology
- **Ex. 15.** Claims 1-3, 6-10, 13-22, and 24 are obvious over Fluidigm Access Array in view of the knowledge of a person of ordinary skill in the art, and further in view of the '575 Publication and/or NGS Technology
- **Ex. 16.** Claims 1-3, 6-10, 13-22, and 24 are obvious over RainDance PCR Technology in view of the knowledge of a person of ordinary skill in the art, and further in view of Chiu and/or NGS Technology

The above list is not exhaustive, and Natera reserves the right to supplement this list as discovery is ongoing.

Under the Supreme Court's decision in *KSR International, Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007), a "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "Common sense teaches . . . that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teaching of multiple patents together like pieces of a puzzle." *Id.* at 420.

"[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *Id.* at 417.

Motivation to combine any of the identified prior art references, platforms, and/or kits exists within the references themselves, as well as within the knowledge of those of ordinary skill in the art, as reflected in the references identified in Section II. Moreover, it would have been obvious for a person skilled in the art to combine these prior art references, platforms, and/or kits because they address the technical issues in the laboratory workflow for library preparation, genetic sequencing, and molecular diagnostics. Furthermore, the library preparation processes described in the Asserted Claims of the '831 patent are obvious variations of prior library preparation processes and do not exhibit any unexpected results.

In addition, the Asserted Claims recite a method of preparing a library of naturally occurring cell-free fetal and maternal DNA sequences found in a maternal blood sample using well-known and conventional techniques. Every step of the Asserted Claims, including selective enrichment and amplifications using primers, is known in the art. *See, e.g.*, Ex. C (U.S. Patent No. 5,399,491), 1:20–23 (cited on the face of the '831 patent and disclosing that "[t]he selective amplification of specific nucleic acid sequences is of value in increasing the sensitivity of diagnostic and environmental assays while maintaining specificity"); Ex. D (U.S. Patent No. 6,210,891), 9:45–46 (cited on the face of the '831 patent and disclosing that "[t]he [claimed] method can be used to both identify and quantitate selectively amplified DNA fragments"); Ex. E (U.S. Patent Publication No. 2009/0087847), ¶ 273 ("incorporated by reference" in the '831 patent "in [its] entiret[y]" ('831 patent, 7:15–32), and disclosing a method by which a "certain sub-population of nucleic acid sequences from the sample pool is sub-selected or enriched prior to sequencing").

For example, as of January 2010, to analyze fetal chromosomal aneuploidy, a skilled artisan would have been motivated to obtain a maternal blood sample that inherently comprises fetal and maternal cell-free DNA, as taught in many of the prior art references identified above such as Chiu and the '575 Publication. To improve sequencing performance, a skilled artisan would also have been motivated to selectively enrich at least 100 different, non-random polynucleotide sequences on a target

chromosome, as taught in many of the prior art references identified above such as Chiu and the '575 Publication, using singleplex or multiplex PCR, or nested PCR, or any of the targeted enrichment platforms on sale at the time. It would be routine to accomplish such enrichment through the use of three amplification steps, the first of which, according to Illumina's amended infringement contentions, may be universal amplification, and the last of which, also according to Illumina's amended infringement contentions, may be clonal amplification that occurs on the sequencing platform. Further, a skilled artisan would have been motivated to use a next-generation sequencer on sale at that time, such as Illumina's GA sequencer, Roche/454's GS FLX sequencer, or Life Technologies' SOLiD sequencer, to sequence the generated DNA library. As such, a skilled artisan would have been motivated to use the library preparation kits and primers for the respective sequencers, which would add sequencing primer sites and indexing sequences to the DNA polynucleotide sequences through DNA amplification using one or more sets of primers. A skilled artisan would have reasonably expected to generate a library of enriched non-random polynucleotide sequences suitable for sequencing after performing the steps claimed in the '831 patent discussed above.

C. Patent L.R. 3-3(c)

Exemplary combinations of prior art references showing where the limitations of the Asserted Claims of the '831 patent are found in the references are attached hereto as Exhibits 1-14.

D. Patent L.R. 3-3(d)

1. Patent Ineligibility

The claims of the '831 patent are not patent-eligible under 35 U.S.C. § 101 because they are directed to naturally occurring subject matter: preparing a collection or "library" of multiple copies of unaltered, naturally occurring cell-free fetal and maternal DNA sequences found in a maternal blood sample. *See, e.g.*, Dkt. 24; Dkt. 35; Dkt. 41 at 4–6. The claims lack an inventive concept because they recite only well-known, routine, and conventional techniques to "amplify" or copy the DNA sequences of interest, including carrying out multiple amplification cycles and the use of conventional amplification elements like primers, sequencing primer sequences, and indexing sequences. *See, e.g.*, Dkt. 24; Dkt. 35, which are incorporated by reference herein.

2. Indefiniteness

The Asserted Claims of the '831 patent are invalid for failure to meet the definiteness requirement of 35 U.S.C. §112, ¶ 2 because they fail to inform a person of ordinary skill in the art with reasonable certainty about the scope of the invention.

For example, the claims are vague and indefinite as to the number of primers in total that should be used depending on the number of "non-random polynucleotide sequences" to be selectively enriched. Independent claim 1 and its dependent claims recite the limitation "a first . . . amplification comprising at least 100 first primers configured to amplify at least 100 different non-random polynucleotide sequences." First, it is unclear whether the first, second and/or third sets of primers are the same set of primers with amplifications being repeated, or whether each set of primers is different from each other. Second, the scope of the term "primers" is unclear. One hundred primers could not be configured to selectively amplify at least 100 different non-random polynucleotide sequences via PCR amplification. Rather, 200 primers, or 100 primer pairs, would be needed: one primer pair for each non-random polynucleotide sequence to be selectively amplified. Thus, it is unclear what is meant by the term "primers."

Independent claim 14 and its dependent claims recite the limitations "amplifying . . . using a first pair of primers," "amplifying . . . with a second set of primers" and "amplifying . . . with a third set of primers," which are vague and indefinite. First, as discussed above, it is unclear whether the first, second and/or third sets of primers are the same set of primers with amplifications being repeated, or whether the sets of primers are different from each other. Second, it is unclear what is meant by a "first pair" of primers. It is not physically possible for a single pair of primers to amplify at least 100 different non-random polynucleotide sequences. Even if the term "first pair" was intended to encompass multiple copies of the same pair of primers, it is not physically possible to selectively enrich at least 100 different non-random polynucleotide sequences using a single primer pair set. Rather, at least 100 different primer pairs would be needed.

In addition, all of the claims contain a limitation that "said enriching compri[ses]" three amplification steps that follow. First, it is unclear what "said enriching" refers to, the "selectively enriching" at the very beginning of the claim, or the "library of enriched non-random polynucleotide

sequences" closer in space to the "said enriching" term. Second, it is unclear whether the "said enriching" is done with all three amplification steps, some subset of the three amplification steps, one of the first, second, or third amplification steps, or some other unrecited step.

Claim 16 recites the limitation "wherein said indexing sequence distinguishes polynucleotides in the maternal blood sample from polynucleotides in a different sample," which is vague and indefinite. The scope of the term "different sample" is entirely unclear. Specifically, it is unclear whether the different sample is a second sample of the maternal blood sample, a sample that is a maternal blood sample from another patient, a sample that is not blood, or a sample that is a tumor tissue, or something else. The use of this term utterly fails to particularly point out and distinctly claim the subject matter of claim 16.

Claim 17 recites the limitation "wherein said cell-free DNA is from a plurality of different individuals," which is vague and indefinite. The scope of claim 17 is indefinite, where independent claim 14 (from which claim 17 directly depends) already provides for the cell-free DNA being from two different individuals (i.e., the fetus and the mother). For example, it is unclear whether the scope of the "plurality of individuals" is intended to encompass something more than what is already encompassed in claim 14, such as multiple fetuses and a mother.

Further, all the Asserted Claims of the '831 patent recite the limitation "100 different non-random polynucleotide sequences," which is vague and indefinite. This limitation contains terms of degree such as "different" and "non-random." But the patent specification and the prosecution history do not provide any guidance on defining these degrees to determine the objective scopes of these terms.

3. Non-Statutory Double Patenting

The Asserted Claims of the '831 patent are invalid under the doctrine of non-statutory double patenting at least because they are anticipated by and/or rendered obvious byU.S. Patent No. 8,318,430 ("the '430 patent"). Under this doctrine, "[a] later claim that is not patentably distinct from, *i.e.*, is obvious over[ ] or anticipated by, an earlier claim is invalid." *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1374 (Fed. Cir. 2014) (internal quotes omitted) (citations omitted). Specifically, a patent claim is invalid if it creates an "unjustified timewise extension of patent rights." *Id.* Exhibit 11 attached hereto demonstrates how each of the Asserted

Claims of the '831 patent is not patentably distinct from the claims of the '430 patent. Accordingly, the '831 patent creates an "unjustified timewise extension of [the '430 patent's] patent rights," and is therefore invalid for non-statutory double patenting.

4. Unenforceability Due to Terminal Disclaimer

The '831 patent is unenforceable in view of a terminal disclaimer made during prosecution to overcome a double patenting rejection based on the '430 patent discussed above. Illumina has failed to comply with the USPTO's conditions for allowing that terminal disclaimer, and thus the '831 patent is unenforceable based on the terms of that disclaimer.

5. Failure to Satisfy Written Description and Enablement Requirements

The specification of the '831 patent neither describes nor enables the full scope of the methods recited in the Asserted Claims of the '831 patent, which renders the claims invalid for failure to meet the written description and enablement requirements of 35 U.S.C. § 112, ¶ 1.

a) Lack of Enablement

A patent's teaching must enable the full scope of the claims. *Sitrick v. Dreamworks, LLC,* 516 F.3d 993, 999 (Fed. Cir. 2008); *In re Fisher,* 427 F.2d 833, 839 (1970). Open-ended claims are subject to the same requirement that disclosure be commensurate to their broad scope. *See, e.g., MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1383 (Fed. Cir. 2012) ("The open claim language chosen by the inventors does ***not*** grant them any forgiveness on the scope of required enablement."); *Fisher,* 427 F.2d at 839. Where the use of open-ended terms like "comprising" expands a key limitation of the claimed invention, the unrecited components encompassed by the open-endedness of the claim must be enabled in the specification. *Promega Corp. v. Life Techs. Corp.*, 773 F.3d 1338, 1350 (Fed. Cir. 2014).

The claims of the '831 patent are open ended. In particular, the claims recite preparing a sequencing library comprising selectively enriching "at least 100 different non-random polynucleotide sequences," comprising a first amplification step in which "at least 100 first primers" are used to amplify "at least 100 different non-random polynucleotide sequences." The claims involve/encompass multiplexing, or the amplification of multiple target sequences in a single reaction, and have a lower bound for the number of target sequences for amplification (or multiplex), but no upper bound.

Therefore, the claims encompass 1000-plex, 20,000-plex, 100,000-plex PCR, all the way to infinity-plex PCR. Indeed, Illumina claims that Natera's Panorama™ process infringes the '831 patent claims, as the Panorama™ library preparation process allows for the targeting of *more than 20,000* genomic variations (i.e., more than 20,000 target sequences) simultaneously in a single test reaction (https://www.natera.com/science-informatics).

In contrast to the claim language, the '831 patent disclosure is very narrow. The patent specification generally discusses massively parallel sequencing techniques, but teaches nothing to advance the development of new, higher multiplexes as do, for example, Natera's U.S. Patent Publication Nos. 2014/0094373 and 2012/0122701. Nor does it disclose multiplexes of 20,000 or higher. 20,000-plex PCR is an order of magnitude over what was well-known, routine and conventional as of January 23, 2010.

The Asserted Claims cover thousands, millions and even infinite numbers of undisclosed embodiments in an unpredictable field without commensurate teaching in the specification. To the extent it is even possible to enable the full scope of the Asserted Claims, undue experimentation would be required. As such, the '831 patent claims are invalid for lack of enablement. *See Promega*, 773 F.3d at 1349; *Magsil*, 687 F.3d at 1383; *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385 (Fed. Cir. 2013).

In addition, independent claim 1 and its dependent claims recite the limitation "a first . . . amplification comprising at least 100 first primers configured to amplify at least 100 different non-random polynucleotide sequences." Undue experimentation would have been required to enable the full scope of coverage sought by Illumina, that is, for example, configuring 100 primers to selectively amplify at least 100 different non-random polynucleotide sequences via PCR amplification. Rather, 200 primers, or 100 primer pairs, would be needed: one primer pair for each non-random polynucleotide sequence to be selectively amplified. As such, these claims are invalid for lack of enablement.

Finally, independent claim 14 and its dependent claims recite the limitation "amplifying . . . using a first pair of primers." Undue experimentation would have been required to enable the full scope of coverage sought by Illumina, that is, for example, configuring a single pair of primers to selectively

amplify at least 100 different non-random polynucleotide sequences. Even if the term "first pair" was intended to encompass multiple copies of the same pair of primers, it is not physically possible to selectively enrich at least 100 different non-random polynucleotide sequences using a single primer pair set. Rather, at least 100 different primer pairs would be needed. As such, these claims are invalid for lack of enablement.

b) Lack of Written Description Support

"The test under the written description requirement is 'whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.'" *Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1351 (Fed. Cir. 2011) (citing *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)).

The Asserted Claims of the '831 patent are invalid for failure to meet the written description requirement. The claims describe preparing a DNA sequencing library using at least three DNA amplification steps with three sets of primers. But the patent specification fails to demonstrate that the inventors actually possessed the claimed inventions. For example, for the first amplification step, independent claim 1 and its dependent claims recite the limitation "a first . . . amplification comprising at least 100 first primers configured to amplify at least 100 different non-random polynucleotide sequences." The patent specification does not describe any DNA library preparation process that configured 100 first primers to amplify at least 100 different non-random polynucleotides for the first DNA amplification step, followed by two more DNA amplification steps.

Similarly, for the first amplification step, independent claim 14 and its dependent claims recite the limitation "amplifying said plurality of non-random polynucleotide sequences from said maternal and fetal genomic DNA using a first pair of primers, wherein said plurality of non-random polynucleotide sequences comprises at least 100 different non-random polynucleotide sequences selected from a chromosome tested for being aneuploid." But the patent specification does not describe any DNA library preparation process that configured a first pair of primers to amplify at least 100 different non-random polynucleotides for the first DNA amplification step, followed by two more DNA amplification steps.

Furthermore, based on Illumina's assertion that clonal amplification may constitute the third amplification step of claims 1 and 14, the '831 Patent lacks written description for clonal amplification constituting that step. The '831 Patent discusses clonal amplification only in the context of DNA sequencing, and never suggests that clonal amplification could constitute the third amplification step of the claims. *see, e.g.*, '831 Patent at 10:53–11:7, 11:38–57, 11:64–12:14, all in the "Sequencing Methods" section of the patent; *see also id.* at 3:31–33 ("said sequencing . . . further comprises bridge amplification[1]"; *id.* at 3:45–47 ("In another embodiment, the isolate genomic DNA are sequenced by a method comprising bridge amplification"). Clonal amplification is not even mentioned in the "Library Formation" section of the '831 Patent (*see id.* at 14:30–22:55), let alone described as the third amplification step of the claims. Instead, the only example disclosing three amplification steps describes three steps of "Nested PCR for DNA Library Construction" (*id.* at 22:4–57), the third step of which is *not* clonal amplification.

Based on Illumina's assertion that universal amplification may constitute the first amplification step of claim 14, the '831 Patent lacks written description for universal amplification constituting that step. The '831 Patent never mentions universal amplification, but rather focuses on ***selective*** amplification steps. *See, e.g.*, '831 Patent at 2:45–56, 4:41–47, 5:66–6:14, 6:44–10:31, 15:25–22:57.

Claims 6 and 7 limit the purported invention of independent claim 1 to a library preparation process where the plurality of non-random polynucleotide sequences is at least 300 and 500, respectively. But the patent specification does not describe any DNA library preparation process of claim 1 where the plurality of non-random polynucleotide sequences is at least 300 and 500. Likewise, claims 8 and 9 limit the purported invention to a library preparation process where each of the plurality of non-random polynucleotide sequences is from 10 to 500 and 50 to 150 nucleotide bases in length, respectively. But the patent specification does not describe any DNA library preparation process of claim 1 where each of the plurality of non-random polynucleotide sequences is from 10 to 500 and 50 to 150 nucleotide bases in length.

[1] Bridge amplification is one type of clonal amplification.

Similarly, claims 18 and 19 limit the purported invention of independent claim 14 to a library preparation process where the plurality of non-random polynucleotide sequences is at least 300 and 500, respectively. But the patent specification does not describe any DNA library preparation process of claim 14 where the plurality of non-random polynucleotide sequences is at least 300 and 500. Likewise, claims 20 and 21 limit the purported invention of claim 14 to a library preparation process where each of the plurality of non-random polynucleotide sequences is from 10 to 500 and 50 to 150 nucleotide bases in length, respectively. But the patent specification does not describe any DNA library preparation process of claim 14 where each of the plurality of non-random polynucleotide sequences is from 10 to 500 and 50 to 150 nucleotide bases in length.

Dated: _____, 2019

Respectfully Submitted,

/s/ Tracey B. Davies

Tracey B. Davies (*pro hac vice*)
tdavies@gibsondunn.com
Mark Reiter (*pro hac vice*)
mreiter@gibsondunn.com
GIBSON, DUNN & CRUTCHER LLP
555 Mission Street, Suite 3000
San Francisco, CA 94105-0921
Telephone: 415.393.8200
Facsimile: 415.393.8306